

1 Amendment to the Specification

2 In the Specification:

3 Please amend the specification as follows:

4 On Page 11, the last paragraph on the page paragraph beginning at line 24 should be replaced  
5 with the following.

6 Because it is anticipated that the present invention will be particularly useful in  
7 research environments that do not require large volumes of product to be generated, it  
8 is anticipated that a reaction module that incorporates a microreactor will be  
9 particularly suitable. Such a microreactor is described in commonly assigned, co-  
10 pending U.S. Patent Application, Serial No. 09/496,999, entitled "MINIATURIZED  
11 REACTION APPARATUS," which was filed February 3, 2000, the disclosure ~~in the~~  
12 ~~specification and drawings~~ (including the specification and drawings) of which is  
13 hereby specifically incorporated herein by reference. Furthermore, a suitable reaction  
14 module is described in commonly assigned, co-pending U.S. Patent Application, Serial  
15 No. 09/578,224, entitled "~~AMENDMENT AND REQUEST FOR~~  
16 ~~RECONSIDERATION~~ MODULAR CHEMICAL PRODUCTION SYSTEM  
17 INCORPORATING A MICROREACTOR," which was filed on May 24, 2000, the  
18 disclosure ~~including in the specification and drawings~~ (including the specification and  
19 drawings) of which is hereby specifically incorporated herein by reference.

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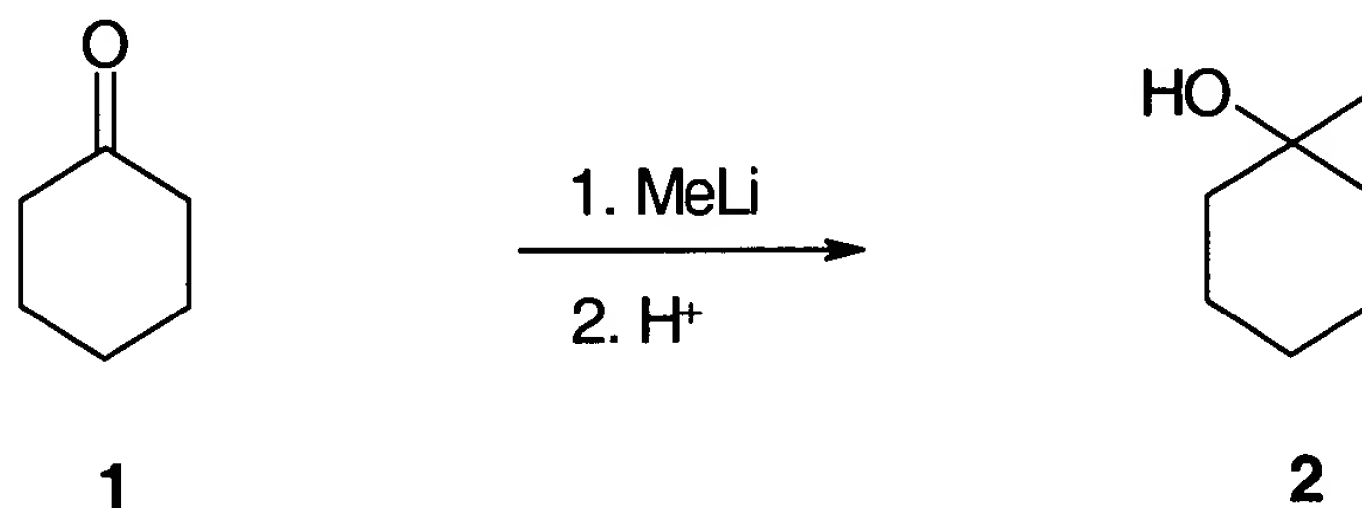
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1 On Page 29, immediately before the final paragraph of the Description of the Preferred  
2 Embodiment, please add the following paragraphs (which are not new matter, as the added  
3 paragraphs are from U.S. Patent Application, Serial No. 09/496,999, which was specifically  
4 incorporated by reference in the present application when the application was originally filed).

5 Exemplary Chemical Reaction Performed in a Stacked Simple Plate Reactor



12 The described chemical reaction belongs to the class of organometallic  
13 conversions, i.e., the addition of an organolithium compound to a carbonyl compound.  
14 Cyclohexanone (1) reacts in a one step procedure with methyl lithium to produce the  
15 1,2-addition product 1-methyl-cyclohexanol (2).

16 Supply of the Starting Materials:

- 17 1. A 1.5 molar solution of methyl lithium dissolved in diethylether  
18 (commercially available in 100-ml bottles sealed with a septum).  
19 2. Preparation of 100 ml of a solution of 13.2 grams (0.15 moles) of  
20 cyclohexanone (commercially available liquid) in dry diethylether.

21 Solution No. 2 is transferred into a pressure compensated bottle with tube  
22 connectors. Both solutions are connected to an argon atmosphere prior to use to avoid  
23 hydrolysis with air.

24 Thermal Conditioning and Setting up of the System:

25 The reactor temperature is adjusted to  $-20^{\circ}\text{C}$  by cryostats, which are connected  
26 to the heat exchangers of the reactor. Solvent (diethylether) is pumped continuously  
27 through the complete system until the solvent flow leaving the reactor has reached  $-$   
28  $20^{\circ}\text{C}$ .

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1                   Performing the Reaction:

2                   After reaching thermal equilibrium, the two-reactant solutions are transferred  
3 by individual pumps via Teflon<sup>TM</sup> tubing into the reactor. The pump rate is set to  
4 1 ml/min for each reactant. The two reactant flows are each divided into four parallel  
5 laminar flow streams with dimensions of several micrometers. They enter the inter-  
6 digital-mixer located under heat exchanger 1, which is a cross flow type heat  
7 exchanger, where they are cooled to the appropriate temperature (-20°C). It should be  
8 noted that this temperature is a function of the desired reaction. In some cases, each  
9 reactant may require pre-treatment to obtain a different reactant temperature. Thus,  
10 the stacked simple plate reactor may preferably include a heat exchanger for  
11 modifying the temperature of each reactant. Of course, if the reactant temperatures are  
12 to be the same, then a stacked simple plate reactor can be designed with a single heat  
13 exchanger to pretreat both reactants.

14                  In the inter-digital-mixer, the two reactant flows are each divided again into 12  
15 individual laminar flow streams for each reactant. These 24 streams enter the four  
16 lamination channels in groups of six streams, where each group of six streams are  
17 combined again (stacked onto each other). From here, the four groups of six stacked  
18 fluid streams enter the four mixing chambers (which are placed under heat exchanger  
19 2), and the four groups of six stacked fluid streams are reduced in thickness so that  
20 diffusion mixing will occur. Thus, in each of the four groups of six stacked fluid  
21 streams, three single streams of reactant A are united with three single streams of  
22 reactant B. After mixing, the reactants exit the four mixing chambers at two exits per  
23 mixing chamber, thus resulting in eight mixed reactant streams. These eight mixed  
24 reactant streams enter the eight reaction channels, which are sandwiched between heat  
25 exchangers 3 and 4. It is within the reaction channels that the final reaction takes  
26 place, and it is here that the most heat is generally produced; thus the reaction  
27 channels are sandwiched between two heat exchangers.

28                  Heat transfer is extremely efficient due to the high surface to volume ratio, to  
29 the selection of an extremely thermally transparent material for the simple plates that  
30 form the heat exchanger (by the control of the material and/or the thickness of the

1 simple plates), and to the thinness of the simple plates (the distance between the  
2 mixing zone and heat exchanger is in the range of a few micrometers). Thus, the heat  
3 of the exothermic reaction can be reduced to 1-2°K above the determined reaction  
4 temperature.

5 The internal volume of the mixing zone is approximately 1 ml, providing a  
6 residence time of 30 seconds, during which the majority of the reaction is completed.  
7 For reactions that need a longer reaction time, an additional residence time chamber  
8 can be added to the reactor, either by using additional simple plates, or by adding a  
9 separate residence chamber module downstream of the reactor.

10 The resultant product stream leaves the reactor via a Teflon™ tube into a  
11 collection flask that is filled with 2N hydrochloric acid. Instant quenching of the  
12 addition adduct and excess reagent takes place.

#### 13 Benefits of the Simple Plate Stacked Reactor:

14 Advantages of the stacked simple plate reactor system are precise temperature  
15 control, exact adjustment of reaction time, and eliminating the need of a protective  
16 atmosphere, since the reactor is a closed environment. Enhanced safety is provided  
17 due to the small quantities of material, and the closed environment operating  
18 conditions.

19 The system is especially advantageous when large quantities of product are  
20 required, because the reactor can work continuously, and can be operated for hours,  
21 even up to days, without maintenance. Accordingly, automated production of large  
22 amounts of the desired product without the loss of efficiency and safety can be  
23 achieved. Additional product can be obtained by operating additional reactors in  
24 parallel under identical operating conditions.

#### 25 System Description:

26 The reactants are provided in conventional laboratory bottles with tube  
27 connectors. The bottles are connected to a pump module by Teflon™ tubes. Inside a  
28 pump module disposed upstream from the pumps are three way valves, which are  
29 connected to the reactants, the solvents, and the pump inlet. For conditioning the  
30 stacked simple plate reactor, the valves are set to the solvents, so that the pumps first

1 fill the whole system with solvent until the stacked simple plate reactor reaches  
2 thermal equilibrium. Then the valves are set to the reactants, enabling the pumps to  
3 deliver the reactants into the stacked simple plate reactor. A filter is placed inline  
4 between the pump outlet and reactor inlet to avoid clogging of the system by  
5 particulates. Fluidic connection of pumps and reactor can be achieved by  
6 commercially available HPLC fittings. Controlling the temperature of the stacked  
7 simple plate reactor is achieved by pumping heat transfer media from a cryostat into  
8 the internal heat exchangers of the stacked simple plate reactor. Product coming out  
9 of the system is collected in a conventional laboratory bottle.

#### 10 Measuring and Automation Control Devices:

11 All pumps, valves, and cryostats are preferably controlled by a microcontroller  
12 or computer, programmed with appropriate software, enabling convenient adjustment  
13 and control of the system. The following sensor devices are optionally used to provide  
14 analog signals that are converted to digital signals for input to the microcontroller or  
15 computer, to facilitate more efficient manual or automated control of the chemical  
16 process:

- 17 • Pressure sensors disposed downstream from each pump and at the inlet  
18 and outlets of the stacked simple plate reactor.
- 19 • Temperature sensors integrated in the stacked simple plate reactor and  
20 disposed close to the mixing zone and at the reactor outlet.
- 21 • Optional flow sensors introduced into each reactant stream for  
22 improved flow adjustment.
- 23 • Excellent control and adjustment of flow and ratio of the reactants,  
24 determination of the pressure buildup inside the system by differential  
25 pressure measurement, and exact adjustment and control of the reaction  
26 temperature can thus be achieved.